MAGNETIC RESONANCE IMAGING OF HUMAN BRAIN FUNCTION

Principles, Practicalities, and Possibilities

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Recent advances in the understanding of human brain have come about in a large part as a result of a combination of the availability of new functional imaging techniques, and no less importantly, creative and careful experimentation. The implementation of new brain imaging techniques has allowed for faster, cheaper, and more effective diagnoses and treatments of neurological, cognitive, or neurophysiologic pathologies. The most recently developed brain activation imaging methods to emerge have been those that use MR imaging. These MR imaging-based techniques have been collectively termed *functional MR* (fMR) *imaging*.

Use of fMR imaging has grown explosively since its discovery by Kwong et al[118] in 1991. Some reasons for this explosive growth include the noninvasiveness of fMR imaging, the wide availability of MR scanners capable of fMR imaging, and the relative robustness and reproducibility of fMR imaging results. With these reasons for using fMR imaging came a proportional need for caution. The technology can be easily misused, and results can be overinterpreted. It is absolutely essential for all fMR imaging practitioners to have at least a basic understanding of the essentials of fMR imaging, which include the related physics, physiology, postprocessing, pulse sequences, and hardware. With a greater understanding of these essentials, it is hoped that innovative clinicians will pave the way for more extensive applicability of fMR imaging. In this article, basic concepts behind fMR imaging are clarified, several practical issues related to its use are discussed and referred to, and potential innovations regarding fMR imaging use are suggested. This article is organized into four sections. First, the types of hemodynamic contrasts observable with fMR imaging are described. Second, ubiquitous issues of fMR imaging implementation are discussed. Third, several of the most common platforms for performing fMR imaging are described. Lastly, current fMR imaging applications are mentioned.

HEMODYNAMIC CONTRAST

Several types of cerebrovascular information can be mapped using MR imaging. The tomographic information that can be obtained include maps of cerebral blood volume[16, 17, 138,

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[159–161] and cerebral perfusion,[53, 63, 109, 119, 190, 195, 196] and maps of changes in blood volume,[16] perfusion,[63, 64, 109, 117–119, 191, 196] and oxygenation.* Following is a description of how these various hemodynamic properties are selectively detected using fMR imaging.

Blood Volume

A technique developed by Belliveau and Rosen et al[17, 159, 161] uses the susceptibility contrast produced by intravascular paramagnetic contrast agents and the high-speed imaging capabilities of echoplanar imaging (EPI) to create maps of human cerebral blood volume (CBV). A bolus of paramagnetic contrast agent is injected (the technique is slightly invasive) and T2- or T2*-weighted images are obtained at the rate of about one image per second using EPI.[46, 63, 128, 175] As the contrast agent passes through the microvasculature, susceptibility gradients (magnetic field distortions) are transiently produced. These gradients, which last the amount of time that it takes for the bolus to pass through the cerebral vasculature, cause intravoxel dephasing, resulting in a signal attenuation that is linearly proportional to the concentration of contrast agent,[159, 161, 188] which in turn is a function of blood volume.

Changes in blood volume that occur during hemodynamic stresses or during brain activation can then be created by subtraction of two maps: one during a "resting" state and one during a hemodynamic stress or neuronal activation.[16] The use of this method marked the first time that hemodynamic changes accompanying human brain activation were mapped with MR imaging.

Blood Perfusion

An array of new techniques now exist for mapping cerebral blood perfusion in humans. The MR imaging techniques are similar to those applied in other modalities, such as positron emission tomography (PET) and single-photon emission-computed tomography (SPECT), in that they all involve arterial spin labeling. The MR imaging-based techniques hold considerable promise of high-spatial resolution without the requirement of contrast agent injections. They use the fundamental idea of magnetically tagging arterial blood outside the imaging plane and then allowing flow of the tagged blood into the imaging plane. The radio frequency (RF) tagging pulse is usually a 180-degree pulse that "inverts" the magnetization.

Generally, these techniques can be subdivided into those which use continuous arterial spin labeling, which involves continuously inverting blood flowing into the slice,[190] and those which use pulsed arterial spin labeling, periodically inverting a block of arterial blood and measuring the arrival of that blood into the imaging slice. Examples of these techniques are "echo planar imaging with signal targeting and alternating RF (EPISTAR)" (Fig. 1*A*), which involves alternately inverting slabs of magnetization above and below the imaging slice,[63, 64] and "flow-sensitive alternating inversion recovery (FAIR)" (Fig. 1*B*), which involves the alternation between slice-selective and nonslice-selective inversion. The latter was introduced by Kwong et al[117, 119, 120] and referred to as FAIR by Kim et al.[109] Recently, a pulsed arterial spin labeling technique known as "quantitative imaging of perfusion using a single subtraction (QUIPSS)," has been introduced.[195, 196] In the case of the pulsed techniques, pairwise subtraction of sequential images (Fig. 1C), with and without the application of the RF tag outside the plane, gives a perfusion-related signal.

Variation of the delay time between the inversion or tag outside the imaging plane and the acquisition of the image gives perfusion maps highlighting blood at different stages of its delivery into the imaging slice. Because there is necessarily a gap between the proximal tagging region and the imaging slice, there is a delay in the time for tagged blood to reach the arterial tree; this delay time can be highly variable, ranging from about 200 ms to about 1 s for a gap of 1 cm. At 400 ms, typically only blood in larger arteries has reached the slice, and the pulsed arterial spin labeling signal is dominated by focal signals in these vessels, whereas at 1000 ms tagged blood has typically begun to distribute into the capillary beds of the tissue in the slice. Images acquired at late inversion times can be considered qualitative maps of perfusion. Figure 2 shows perfusion maps created at different TI times using both the FAIR and the EPISTAR technique. As TI is lengthened, tagged blood distributes from

* References 12, 29, 74, 106, 118, 144, 145, 146, 176, 181, and 182.

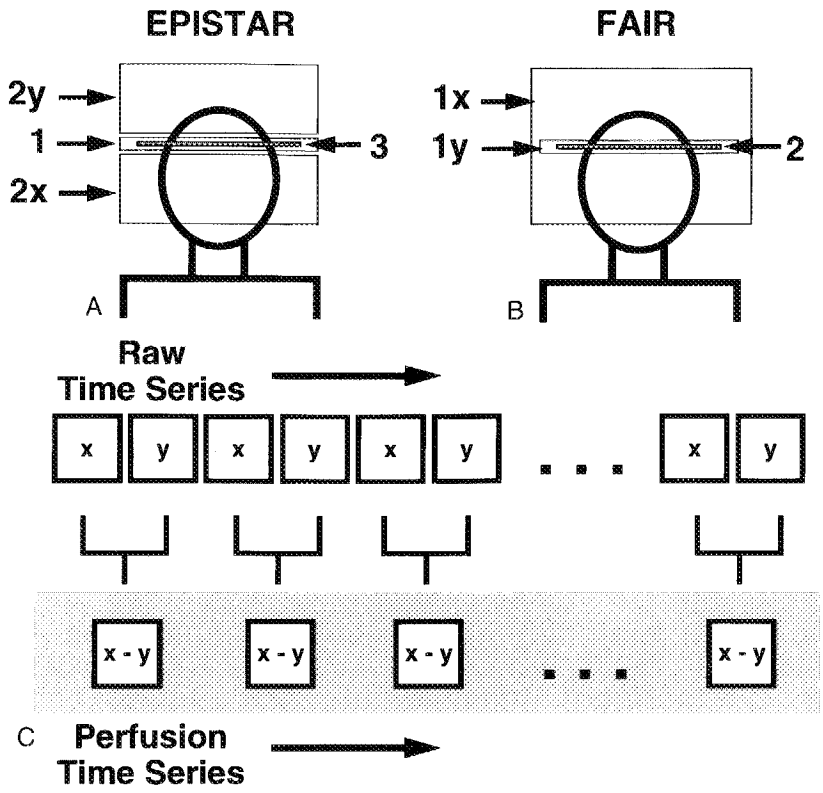

Figure 1. The process by which MRI perfusion images are created. *A*, Echo planar imaging with signal targeting and alternating RF (EPISTAR). The imaging slice is presaturated with a saturation pulse (1). Then, protons above and below the imaging plane are alternately inverted or tagged (2x, 2y). The image is then collected after a delay time to allow the tagged protons to perfuse into the imaging plane (3). Alternate images collected in the sequential time series correspond to either the tag below (2x) or above (2y) the plane. *B*, Flow-sensitive alternating inversion recovery (FAIR). Protons either within the plane or everywhere are alternately inverted or tagged (1x, 1y). The image is then collected after a delay time to allow the tagged protons (1x) to perfuse into the imaging plane. Alternate images collected in the sequential time series correspond to either the tag everywhere (1x) or only within (1y) the imaging plane. *C*, The method by which the time series of perfusion images is created from the pulse sequences shown in A and B. The alternate images, x and y, are collected in time. These images, with different tags applied, are different only in the degree to which flowing spins contribute to the signal. Therefore, a perfusion-signal-only time series of images is created by pairwise subtraction of the images.

large arteries into smaller vessels and capillary beds. In the capillaries, the tagged blood water exchanges almost completely with tissue water. To quantify perfusion using these techniques it is necessary to more carefully model the phenomena and relevant variables.[36, 40, 109, 119] For quantification, a minimum of two subtractions at different TIs are required to calculate the rate of entry of tagged blood into the slice (perfusion).[36]

For the application of mapping of human brain activation (i.e., to only observe activation-induced changes in blood perfusion), a more commonly used flow-sensitive method is performed by application of the inversion pulse, always in the same plane. In this case, the intensity of all images obtained will be weighted by modulation of longitudinal magnetization by flowing blood and also by other MR parameters that normally contribute to image intensity and contrast (proton density, T1, T2). Therefore, this technique allows only for observation of changes in flow that occur over time with brain activation. This technique was first implemented by Kwong et al[118] to observe activation-induced flow

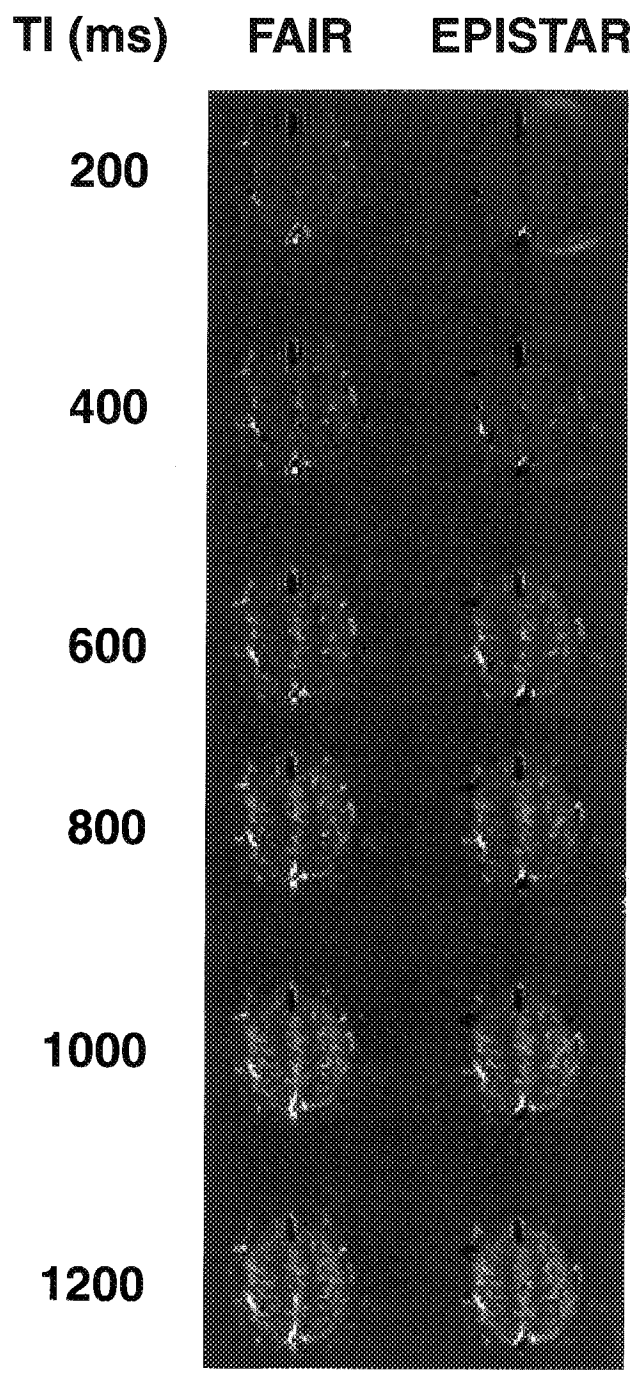

Figure 2. Comparison of EPISTAR and FAIR at corresponding delay time (T1) values. As delay time is lengthened, tagged blood distributes from large arteries into smaller vessels and capillary beds. In the capillaries, the tagged blood water exchanges almost completely with tissue water. Short delay times highlight rapidly flowing blood, and the long delay times highlight capillary bed perfusion.

changes in the human brain. In this seminal paper, activation-induced signal changes associated with local changes in blood oxygenation were also observed.

Blood Oxygenation

In 1990, pioneering work of Ogawa et al[144, 145, 146] and Turner et al[182] demonstrated that MR signal in the vicinity of vessels and in perfused brain tissue decreased with a decrease in blood oxygenation. This type of physiological contrast was coined "blood oxygenation level dependent" (BOLD) contrast by Ogawa et al.[145]

The use of BOLD contrast for the observation of brain activation was first demonstrated in August of 1991, at the 10th Annual Society of Magnetic Resonance in Medicine meeting.[51] The first papers demonstrating the technique, published in July 1992, reported human brain activation in the primary visual cortex[118, 148] and motor cortex.[12, 118] Two[12, 118] of the first three reports of this technique involved the use of single-shot EPI at 1.5 Tesla. The other[148] involved multishot "fast low angle shot" (FLASH) imaging at 4 Tesla. Generally, a small local signal increase in activated cortical regions were observed using gradient echo pulse sequences, which are maximally sensitive to changes in the homogeneity of the main magnetic field.

The working model constructed to explain these observations with gradient-echo imaging was that an increase in neuronal activity causes local vasodilatation which, in turn, causes an increase in blood flow. This results in an excess of oxygenated hemoglobin beyond the metabolic need, thus reducing the proportion of paramagnetic deoxyhemoglobin in the vasculature. This hemodynamic phenomenon was previously suggested using non-MR imaging techniques.[70, 80, 84] A reduction in deoxyhemoglobin in the vasculature causes a reduction in magnetic susceptibility differences in the vicinity of venules, veins, and red blood cells within veins, thereby causing an increase in spin coherence (increase in T2 and T2*), and therefore an increase in signal in T2*- and T2-weighted sequences.

Presently, the most widely used fMR imaging technique for the noninvasive mapping of human brain activity is gradient-echo imaging using BOLD contrast. The reasons for this are that gradient-echo T2*-sensitive techniques have demonstrated higher activation-induced signal change contrast by about a factor of two to four than T2-weighted, flow-sensitive, or blood volume-sensitive techniques, and BOLD contrast can be obtained using more widely available high-speed multishot non-EPI techniques. Although T2*-weighted techniques are sensitive to blood oxygenation changes in vascular structures that include large vessels that may be spatially removed from the focus of activation, for most applications the sacrifice in functional contrast-to-noise ratio in techniques more sensitive to microvascular structures does not outweigh the necessity for the highest possible contrast-to-noise ratio in functional images. Successful implementation of fMR imaging begins with a knowledge of the hemodynamic contrast that can be detected. An understanding of several ubiquitous fMR imaging issues is also critical.

UBIQUITOUS ISSUES OF fMR IMAGING

Although progress is being rapidly made, many issues in fMR imaging remain incompletely understood. Following is a description of the current state of understanding regarding some general fMR imaging issues, categorized into interpretability, sensitivity, and some unknowns that remain to be resolved.

Interpretability

The question of interpretability regards the concern of exactly what the relationship is between the fMR imaging signal and underlying neuronal activation. Two "filters" separate direct observation of neuronal processes using fMR imaging. The first is the relationship between neuronal activation and hemodynamic changes, and the second is the relationship between hemodynamic changes and MR signal changes.

When a population of neurons experiences membrane polarity changes during activation, measurable electrical and magnetic changes in the brain are created.[90, 95, 115, 159] Because of the energy requirements of membrane repolarization and neurotransmitter synthesis, brain activation also causes a measurable increase

in neuronal metabolism.[72, 91, 129, 136, 150, 151, 158] Through incompletely understood mechanisms[34, 83, 115, 116, 127, 131, 140, 158, 184] these changes are accompanied by changes in blood flow,* volume,[16, 70, 164, 184, 185] and oxygenation.[70, 79, 80, 84, 184, 185] It is not known whether these changes are constant across tasks and across regions in the brain, or exactly what mediates them.

Over the past 5 years, considerable progress has been made in the characterization of the second relationship—that between activation-induced hemodynamic changes and the fMR imaging signal changes. To follow, the issue of MR imaging-achievable hemodynamic specificity is discussed. Also discussed are the upper limits of temporal and spatial resolution, and the dynamic range of fMR imaging.

Hemodynamic Specificity

A high priority in fMR imaging is to accurately correlate activation-induced MR signal changes with underlying neuronal processes. It is generally accepted that perfusion and oxygenation changes in capillaries are closer in both space and time to neuronal activation than those arising from arteries or veins. As mentioned, different pulse sequences can be made sensitive to specific populations of vessel sizes, blood flow velocities, and contrast mechanisms.

The fMR imaging pulse sequence that gives the highest functional contrast-to-noise ratio is a T2*-weighted gradient-echo sequence, which is likely to have contrast weighting, which includes large draining vein effects and, in the case of short TR-high flip angle sequences (short TR values are required for non-EPI fMR imaging sequences), large vessel arterial inflow effects. Sequences that may be able to more selectively observe capillary oxygenation or perfusion effects are less robust. They have a lower functional contrast-to-noise ratio, are generally less time efficient, and may not allow extensive multislice imaging. The tremendous need for high fMR imaging contrast-to-noise ratio, high-image acquisition speed, and high flexibility, such as multislice imaging, has to date outweighed the need, in most cases, for selective observation of capillary effects for most applications. Enhancements in fMR imaging sensitivity may allow these hemodynamically selective pulse sequences to be more commonly used. The strategies for achieving hemodynamic specificity not only include pulse sequence modifications but also simple vein and artery identification strategies or even activation strategies which remove draining vein effects. To follow, several of the more common pulse sequences and paradigm strategies for obtaining higher hemodynamic specificity are listed in alphabetical order and described. These methods can be considered as relevant to the goals summarized in Table 1.

Angiography.[125, 135] Use of standard high-resolution angiographic techniques can identify rapidly flowing blood. Advantages are that it can be performed relatively quickly and independently of the functional imaging series; disadvantages are that blood in larger arteries are visualized, but slowly flowing venous blood may be missed.

Asymmetric Spin-echo.[1] This technique involves the use of a spin-echo, but with the readout window shifted from the spin-echo center (asymmetrically located) so that similar susceptibility (T2′) weighting as a gradient echo sequence is achieved. Advantages are that rapidly flowing blood does not experience the 180-degree pulse, applied about 40 ms after the 90-degree pulse, and therefore does not contribute to the signal. This phenomenon also reduces some of the pulsatile fluctuations over time. Disadvantages are that the use of a spin-echo increases imaging time by about 100 ms, which may limit the number of slices (in space) obtained in a TR using EPI. This time cost for non-EPI sequences (with the possible exception of fast spin echo[50]) is practically prohibitive. This sequence is also equally sensitive as

Table 1. HEMODYNAMIC SPECIFICITY*

Goal	Method Number
Separation of flow and oxygenation effects	Flow: 6, 15; oxygenation: 11, 10, 14; both: 13, 18.
Identification of large arteries and veins	Veins: 4, 5, 7, 11, 14; arteries and veins: 1, 16, 19.
Partial reduction of large artery or vein effects	Veins: 2, 4, 8, 17; arteries and veins: 9, 10.
Selective imaging of capillary effects	Flow: 13, combination of 3 and 13. Oxygenation: 12; combination of 3 and 17.

* Goals regarding the achievement of hemodynamic specificity in fMR imaging and corresponding methods that have been proposed in the literature. The method numbers correspond to the methods listed.

* References 48, 59, 68, 83, 99, 100, 116, 127, 131, 140, 158, and 184.

regular gradient-echo sequences to intravascular effects (T2* dephasing of the blood) from large vessels that have slowly flowing spins and to extravascular effects (spin dephasing that occurs outside of the veins as a result of magnetic field gradients extending from the vessels due to the difference in magnetic susceptibility between the vessels and tissue) of large vessels with intravascular signal that has been removed by the 180-degree pulse.

Diffusion Weighting.[30,173] This technique incorporates additional magnetic field gradients between RF excitation and data acquisition to selectively dephase signal from faster moving populations of spins. Blood having rapid incoherent motion (i.e., blood in larger vessels) within a voxel is dephased, and therefore removed from contributing to the fMR imaging signal change. Advantages include intravascular large vessel effects that cannot be seen using other techniques (possibly because they may be subvoxel in size) are reduced with this technique. Disadvantages include the addition of diffusion weighting reduces the image signal-to-noise ratio and the functional contrast-to-noise ratio, and increases the motion sensitivity over time. This technique can only realistically be performed using EPI. Also, large vessel intravascular effects are not eliminated. Lastly, large vessel extravascular dephasing effects (T2* contrast) are unaffected and therefore may still contribute to fMR imaging signal changes.

High Field Strength.[134,135,181,183] In the context of fMR imaging, a field strength above 2 Tesla is considered high. Advantages are that signal-to-noise theoretically increases linearly with field strength. BOLD-based functional contrast may increase from linearly or sublinearly[13] to almost quadratically.[147,181] Because T1 relaxation rates become longer at high-field strengths, flow imaging techniques[40,63,64,109,117,119,190,195,196] also benefit because of decreased decay of the tag signal. Higher field strength also allows detection of more subtle effects, higher spatial resolution, or less need for averaging over time. Also, the T2* difference between deoxygenated blood and gray matter becomes greater, allowing clear identification of veins as dark spots in high resolution T2*-weighted images.[104,135] Disadvantages are that high-field magnets do not have a large market, and therefore are not as tried and true as lower field clinical workhorses (i.e., more trouble-shooting is needed). The primary practical problem at high fields is the increased field distortion due to magnetic susceptibility effects. This field distortion causes both image distortion and signal dropouts, but because on a microscopic scale it is also the mechanism of BOLD contrast, techniques that are sensitive to BOLD contrast are inherently sensitive to these other deleterious effects. These problems make magnetic field shimming more important at high fields. Because the field distortions can only be partially removed by shimming, they often preclude whole-brain imaging and imaging of structures at the base of the brain. Lastly, physiological fluctuations may increase with field strength, which if not filtered, can increase the noise and nullify the inherent signal-to-noise advantages of high fields. Alternatively, an increase in physiological fluctuations may translate to an advantage if the fluctuations prove to contain useful physiologic or neuronal information.

Hypercapnia Normalization.[3] Because the fractional signal change using BOLD contrast is highly weighted by the distribution of blood volume across voxels, a uniform oxygenation increase, concomitant with a hypercapnia-induced flow increase, would cause the BOLD signal increase in each voxel that is in proportion to underlying hemodynamic variables, primarily venous blood volume. Maps of venous blood volume distribution can be made in this manner. Assuming that hypercapnia and activation cause similar hemodynamic events,[96,118] one global and the other localized to neuronal activation, then division of a "percent change during brain activation" image by a "percent change during hypercapnia" image would give a ratio map of task-induced signal activation that is normalized to the signal change accompanying global vasodilatation. Advantages are that this technique has the potential of normalizing for all hemodynamic variations over space that can modulate the signal given a constant oxygenation change, and not just remove large vessel effects. Disadvantages are division of percent change images obtained in different imaging runs reduces the signal-to-noise significantly, and is also highly sensitive to systematic variations over time. Also, giving a hypercapnic stress test before or after every fMR imaging study is impractical from a time, convenience, and safety viewpoint.

Inversion Recovery.[118] As described previously, an inversion-recovery sequence allows

maximum sensitivity to activation-induced perfusion-related T1 changes. Used with minimally T2- or T2*-sensitive imaging (i.e., short TE spin-echo acquisition), exclusive sensitivity to perfusion is achieved. Advantages are if used with minimally T2- or T2*-sensitive imaging (i.e., short TE spin-echo acquisition), exclusive sensitivity to flow changes is achieved. Disadvantages are that this technique can only be practically used with EPI because the waiting period (TI) is too long for standard multishot fMR imaging techniques. Also, it has lower sensitivity to functional changes than gradient-echo sequences.

Latency Mapping.[123] It is thought that, on activation, larger vessels "downstream" from the activated region become oxygenated at a slightly later time than capillaries or venules. This technique uses this vessel size-specific BOLD contrast latency to identify draining veins. Advantages are this technique can be applied in a post hoc manner, and is relatively easy to implement. Disadvantages are that because of functional contrast-to-noise limitations, latency differences on the order of 1 second require significant averaging to be differentiated. The latency differences between large veins and capillaries may vary, and in many cases, be less than 1 or 2 seconds, therefore making the technique somewhat unreliable. Also, although unlikely, it is possible that some neuronal processes may have latency differences (or hemodynamically transmitted latency differences) on the order of a second,[23] therefore confounding the technique.

Latency Tagging.[56, 67, 170, 178] This is useful for high-resolution mapping of subtle spatial differences in the hemodynamic response as the cortical representation of the stimulus is continuously varied in time. This technique lends itself to high-resolution mapping of contiguous cortical regions. Advantages are that large vessel effects may be reduced since the stimulus is continuously "on," but spatially modulated. Large vessels, receiving flow from a relatively large area, will be in a steadily more oxygen-saturated state. The "spillover" of oxygenated blood is constant, therefore allowing a higher functional spatial resolution by having all the "spillover" effects subtracted out. The highest fMR imaging "functional" resolution reported has been with the use of this technique.[67] The functional contrast per unit time is optimized because the entire time course has information embedded within it. Disadvantages are that this technique does not lend itself to the mapping of regions in which a continuous variation in the stimuli does not cause a continuous variation in the cortical regions activated (i.e., those cortical representations of a time-varying stimuli that do not vary continuously over space).

Long TR (high flip angle) or Short TR (low flip angle).[76, 112] This is a method by which arterial inflow effects are minimized. Differences in steady-state magnetization between the imaging plane and outside of the imaging plane are minimized. Effects elicited by changes in activation-induced inflow (activation causes fresh un-RF–saturated spins to enter the imaging plane at a higher rate) are reduced. Advantages are that these techniques are simple to implement and well understood. Disadvantages are the long TR technique (TR > 1 sec) can only be practically achieved using EPI. Multishot techniques generally need to use a short TR to collect images in a practically feasible time. If a short TR is necessary, reduction of the flip angle below the Ernst angle is suboptimal from a signal-to-noise standpoint.

Outer Volume Saturation.[60–62] This technique is similar, in principle, to the above technique, but instead of the in plane–out-of-plane magnetization difference being decreased by an increase in the in-plane magnetization–the out-of-plane magnetization is reduced. This technique reduces signal not only from inflowing arterial spins, but also inflowing large venous vessel spins. Therefore, only smaller (slower flowing) vein intravascular BOLD effects and large (rapidly flowing) vein extravascular BOLD effects are observed. Advantages are that implementation is straightforward. Disadvantages are the saturation slice profile may interfere with the signal from the slices of interest. Rapidly flowing blood arriving from outside of the saturation plane remains unaffected.

Phase Shift Mapping.[87, 124] If a single vein having a single orientation is located within a voxel, then during a change in oxygenation the resonant frequency within that vessel will change, causing a coherent phase shift within the voxel, depending on the TE. These phase shift effects are not present in voxels containing only randomly oriented capillaries. Visualization of resting-state phase shifts or phase dispersions and activation-induced phase shifts can be used to identify large vessel ef-

fects. Advantages are that this technique is easy to implement. NMR phase images simply need to be created. Disadvantages are that the technique works best with very small voxels, but may miss large vessels due to its sensitivity to vessel orientation.

Pre-undershoot "Dip."[93, 134] Several studies have shown an initial decrease in the fMR imaging signal 0.5[93] to 2 seconds[135] after the stimulus onset, but immediately prior to the increase in signal that is typically observed. These changes are hypothesized to be caused by an increase in oxidative metabolic rate[84, 133] or change in the ionic environment of the neurons[93] occurring at the regions of neuronal activity prior to subsequent flow and oxygenation increases. Advantages are that assuming that the hypothesized origins of this signal behavior are substantiated, observation of this signal would allow localization of neuronal activity with a high degree of spatial and temporal specificity. Disadvantages include that this transient signal can only be observed with high-speed imaging (EPI) or by functional spectroscopy. Secondly, this is an extremely subtle effect and has not been extensively reproduced. High contrast-to-noise ratio with extensive averaging and physiologic noise reduction may be essential to observe this. The pre-undershoot has not yet been demonstrated in any other cortical region but visual cortex.

Spin Tagging Techniques.[40, 63, 64, 109, 117, 119, 190, 195, 196] These include the array of techniques mentioned previously. Flowing spins are imaged by inverting or saturating spins outside the imaging plane, waiting a time period for the tagged spins to flow into the imaging plane, then imaging. Both resting state perfusion and activation-induced perfusion changes can be imaged. Advantages include that this is a noninvasive and robust technique by which quantifiable maps of flow and flow changes can be created. The pulse sequence can be adjusted so that capillary perfusion is selectively imaged. Also, the flow images created are insensitive to oxygenation effects, which translates to a potentially more direct measure of the degree of neuronal activation. Also, because pair-wise subtraction is performed, the images are sensitive to motion occurring only in the brief interval ($\approx$ 2 seconds) between successive images, and much less sensitive to typically problematic motion occurring on longer time scales. Lastly, if each of the image pairs is oxygenation-sensitive (i.e., T2*- or T2-weighted), oxygenation effects can be assessed by observation of every other image in the time series,[109, 191, 195] therefore giving both flow and oxygenation information simultaneously. Disadvantages are that presently only one or very few imaging planes can be imaged at one time. This technique also involves a relatively long waiting period (TR of at least 2 seconds) for each image, and requires that pairs of images are subtracted, therefore reducing the contrast-to-noise per unit time.

Figure 3 shows a comparison of a spin-tagging technique (FAIR) with BOLD contrast functional imaging. Low-resolution (64 $\times$ 64) and high-resolution (128 $\times$ 128) anatomical and functional (correlation maps) BOLD contrast images (gradient-echo, TE = 40 ms) were obtained of an axial slice through the motor cortex. Single-shot EPI was performed using a local gradient coil[193] and a 3T/60 Bruker Biospec scanner (Billerica, MA). The images were 5-mm thick, and the field of view (FOV) was 20 cm. The task was bilateral finger tapping. Resting- and active-state perfusion maps, created using FAIR (TI = 1400, TR = 2 seconds, spin-echo TE = 42 ms), are also shown. A functional correlation map using BOLD contrast at the two different resolutions are compared with a functional correlation map using the FAIR perfusion time course series. The magnified images, shown in Figure 4, illustrate that the areas of activation obtained using FAIR and BOLD contrast generally overlap, but also have some significant differences. These spatial shifts in activation are likely to be due to the differences in hemodynamic sensitizations of the two sequences. FAIR imaging using a TI of 1400 ms is optimally sensitized to imaging capillary perfusion, as shown in the resting- and active-state flow maps. BOLD contrast functional images are strongly weighted by large draining vein effects.

Tailored RF Gradient-echo Sequence.[41] This technique uses a tailored RF pulse that dephases static and flowing tissue in homogeneous fields, but does not dephase tissue in the presence of field inhomogeneities[42] created around vessels containing deoxygenated blood. Advantages are that when used in conjunction with techniques requiring a short TR, inflow effects are suppressed. It may be less sensitive to motion because signal from static tissue is suppressed; therefore, slight misregistration of images will not cause large signal changes. Also, use of this technique allows di-

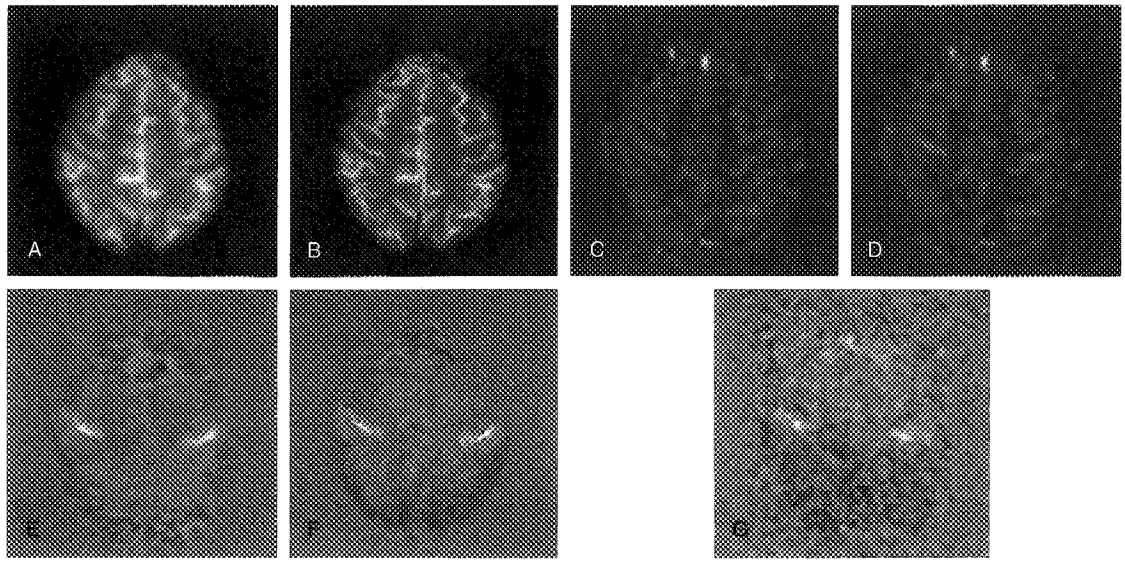

Figure 3. Comparison of perfusion-weighted and BOLD-weighted functional echo planar images at 3 Tesla. Echo planar imaging was performed using a Bruker 3T/60 scanner and a local head gradient coil. All images were created of the same plane in the same experimental session. The slice thickness was 5 mm and the FOV was 20 cm. An axial plane was chosen which contained the motor cortex. *A*, 64 × 64 gradient-echo anatomical image (TE = 50 ms, TR = ∞). *B*, 96 × 96 gradient-echo anatomical image (TE = 50 ms, TR = ∞). *C*, Perfusion image created during the resting state using a FAIR time course series (T1 = 1400 ms, Spin-echo TE = 60 ms, TR = 2 sec). *D*, Perfusion image created from the same time course series as C during bilateral finger tapping. *E*, 64 × 64 BOLD contrast functional correlation image created from the time series of images in which *A* was the first of the series. Bilateral finger tapping was performed. *F*, 96 × 96 BOLD contrast functional correlation image created from the time series of images in which *B* was the first of the series. Bilateral finger tapping was performed. *G*, 64 × 64 perfusion-only functional correlation image created from the same time series of perfusion images from which the resting state and active state images (*C* and *D*) were created. Note the difference in spatial location of the area of activation between the flow-weighted and perfusion-weighted functional images. The "hot spot" in the BOLD contrast images is likely to be a draining vein which does not appear in the perfusion-weighted functional image created using FAIR.

rect visualization of subvoxel inhomogeneities, giving the potential to directly visualize veins. Disadvantages are that it is not clear how implementation of this for fMR imaging is an improvement over simple flip angle reduction for reducing inflow effects. Because no functional images using the technique have yet been published, the robustness of the technique has not been demonstrated.

Short TR, Short TE Spin-echo. This technique is a simple method for achieving T1 weighting, and therefore, flow-sensitive contrast. A short TE spin-echo is minimally sensitive to oxygenation changes, and a short TR gives increased sensitivity to flow changes. Advantages are that this is more time efficient than inversion recovery sequences. It is useful in multishot imaging and when using EPI to sample transient hemodynamic events. Disadvantages are that this technique has half the flow sensitivity of inversion recovery imaging.

Small Voxels with High Signal to Noise Ratio. Reduction of the voxel size makes it more likely that a large vein will completely fill one or several voxels (100% blood volume) whereas the blood volume per voxel from capillaries remains the same (2% to 5% blood volume). With higher resolution and with high enough signal-to-noise at high resolution to visualize subtle capillary effects (≈ 1% signal change at 1.5T), a greater stratification of vessel effects (increase with higher resolution[86]) from capillary effects (insensitive to resolution) is achieved. Advantages are that it is relatively easy to interpret high-resolution and high-functional contrast to noise functional images. Disadvantages are that because of signal-to-noise demands, this technique is likely to be achievable only at higher field strengths or with significant data averaging.

Spin-echo with Long TE.[15,50] Instead of signal being collected immediately after the 90-

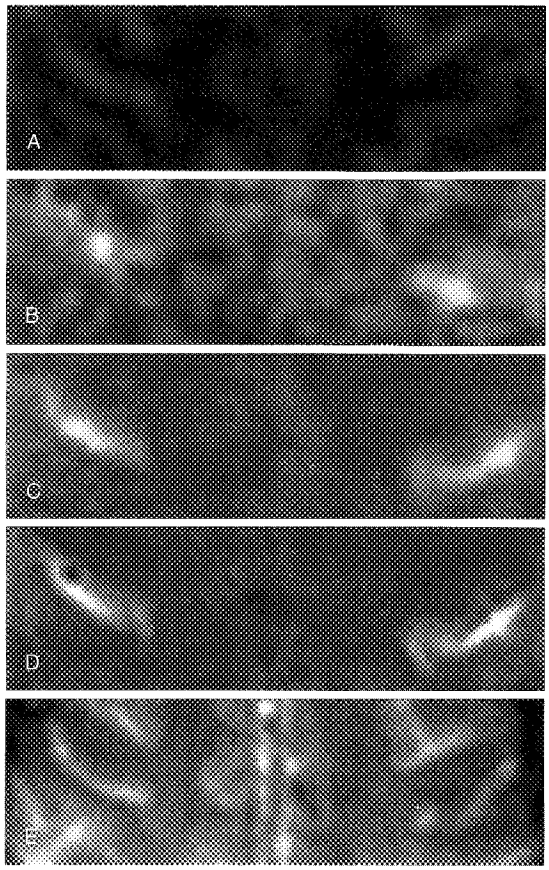

Figure 4. Magnification of selected images displayed in Figure 3 to emphasize the differences in the activation locations that appear with different hemodynamic sensitizations. *A*, Baseline 64 × 64 perfusion image (magnification of 3.C). *B*, 64 × 64 perfusion-only sensitive functional correlation image (magnification of 3.G). *C*, 64 × 64 BOLD contrast functional correlation image (magnification of 3.E). *D*, 96 × 96 BOLD contrast functional correlation image (magnification of 3.F). *E*, 96 × 96 gradient-echo anatomical image (magnification of 3.B). Dark lines in the image are likely to be caused by deoxygenated veins.

degree pulse (during the free induction decay [FID]), data is collected during the echo that occurs after a refocusing (180-degree) pulse is applied. Activation-induced changes in T2 instead of T2* are imaged. Macroscopic susceptibility gradients are refocused by the spin-echo, but susceptibility gradients on the spatial scale of the distance that a water molecule diffuses in an echo time ($\approx$ 10 μm) are not refocused. It is for this reason that spin-echo sequences are thought to be sensitive to susceptibility gradients (and activation-induced changes in susceptibility gradients) caused by small compartments, such as red blood cells and capillaries. Advantages are that extravascular large vessel effects are not seen because the refocusing pulse eliminates the effect of gradients on a spatial scale significantly larger than large vessels. This technique also has the same advantages as technique asymmetric spin-echo. Disadvantages are that with this technique, activation-induced intravascular signal from blood in large vessels flowing slow enough to still experience the 180-degree pulse remains present. Secondly, the functional contrast-to-noise of this technique is about one quarter that of gradient-echo sequences.[14, 15]

TE Stepping.[8, 10, 15, 135] This technique involves the systematic incrementation of the echo time, allowing acquisition of two types of hemodynamic information simultaneously. TE stepping allows direct measurement of T2* (from the slope of a monoexponential fit to the decay curve) and measurement of inflow effects (from the intercept of the monoexponential fit to the decay curve). Advantages are that the simultaneously provided information is useful in that systematic errors that come from measures across trials are avoided. This is useful for studies that require direct registration of individual voxels and for studies in which successive course series can never be identical, such as those involving a hemodynamic stress such as hypercapnia. Disadvantages are that the time cost for this technique is high. The sensitivity of the technique for measuring flow (TE = 0 intercept of R2* curve) is low.

Variance Imaging and Frequency Analysis.[26, 187] This technique involves the collection of a time course series of echo-planar images, then inspecting the series in a voxel-wise manner for noise characteristics. Large vessels seem to cause large MR signal intensity fluctuations at the cardiac and respiratory cycle rates, and are therefore identifiable. Advantages are that it is relatively easy to implement. Disadvantages are that the specificity of the technique is unreliable in that many regions other than large vessels (cerebral spinal fluid) can show large pulsatile effects. Also, Fourier analysis is performed best in conjunction with only the rapid sampling rate of EPI.

Improvements in functional spatial and temporal resolution are still being rapidly made at this stage. The maximum temporal and spatial resolution of fMR imaging can only be fully realized by the combination of a high contrast-to-noise ratio, hemodynamic specificity, significant motion and artifact reduction, and well-controlled and carefully executed experi-

ments. Following is a summary of the issues in achieving high temporal and spatial resolution in fMR imaging.

Temporal Resolution

Two separate time scales are present and separately measurable: the time for the signal transition from one state to another and the accuracy to which the location of the transition can be measured. Because the fMR imaging signal change arises from hemodynamic changes, the practical upper limit on functional temporal resolution is determined by the functional contrast-to-noise ratio and by the variation of the hemodynamic response latency in space and in time.[9, 55, 123, 124, 165] These variations may be due to differences in neuronal activation characteristics across tasks,[23] but are more likely to be due to differences in vessel size[123] or to regional differences in the vascular transit rate. The latency of the hemodynamic response has been described as a shifting and smoothing transformation of the neuronal input.[77] Although this smoothing creates a transition between activation states on the order of 5 to 8 seconds, the accuracy in the measurement of the location of this transition can be much greater, and is limited primarily by variations in the hemodynamic response. The upper limit of temporal resolution discrimination has been empirically determined to be on the order of 1 second[20] or less.[165]

The type of neuronal and hemodynamic information that may be obtained from signals elicited from brief stimuli paradigms may be qualitatively different from the information elicited by longer-duration activation times. Transient activation durations (<1 second) are detectable as MR signal changes which begin to increase 2 seconds after the activation onset, and plateau at 3 to 4 seconds after activation.[9, 166] Figure 5 demonstrates that functional brain maps can be created by repeated activation periods lasting only 2 seconds. Single-shot gradient-echo EPI was performed using the same setup as described previously. The FOV was 20 cm and slice thickness was 5 mm. Matrix size was 96 × 96. A time course series of 1000 axial images (TR = 500 ms, TE = 40 ms) through the motor cortex was obtained during which the subject performed bilateral finger tapping for 2 seconds followed by an 18-second rest; this cycle was repeated for 500 seconds. Figure 5*A* shows the time course from the motor cortex averaged across over time. This plot demonstrates that one limiting factor in upper temporal resolution is the standard deviation of the signal at each point. This variation may be due to the system noise of the hemodynamic variability over time. This plot was then used as the reference function for subsequent correlation analysis. The dot product image (a measure of the magnitude of the signal change[6]) and latency map are shown in Color Plate 2, Figure 11. The latency or delay map shows the relative temporal delay at which the cross-correlation with the reference function was maximized. The latency mapping technique (latency tagging) demonstrates that a "spread" of up to 4 seconds in the hemodynamic response time occurs across space. The histogram of the latencies, shown in Figure 5*B*, and the latency map demonstrate this spread over space. Note also that the regions that show the longest delays also generally show the highest dot product values, and are also the areas that appear as dark spots in the T2*-weighted anatomical image. All of the pieces of information point to the fact that these areas are "downstream" large draining vein effects.

For many types of investigations it may be desirable to use experimental paradigms similar to those used in event related potential recordings (ERP) or magneto-encephalography (MEG),[149] in which multiple runs of transient stimuli are averaged together. For this type of paradigm (requiring rapid sampling), EPI is optimal. As a side note, because of the brief collection of time of EPI relative to typical TR values (e.g., 50 ms relative to about 1 sec), the between-image waiting time allows for performance of EEG in the scanner during the imaging session without electrical interference from MR pulse sequences.[101]

Spatial Resolution

The upper limit on functional spatial resolution, similar to the limit on temporal resolution, is likely determined not by MR imaging resolution limits, but by the hemodynamics through which neuronal activation is transduced. Evidence from in vivo high-resolution optical imaging of the activation of ocular dominance columns[79, 80, 84] suggests that neuronal control of blood oxygenation occurs on a spatial scale of less than 0.5 mm. MR evidence

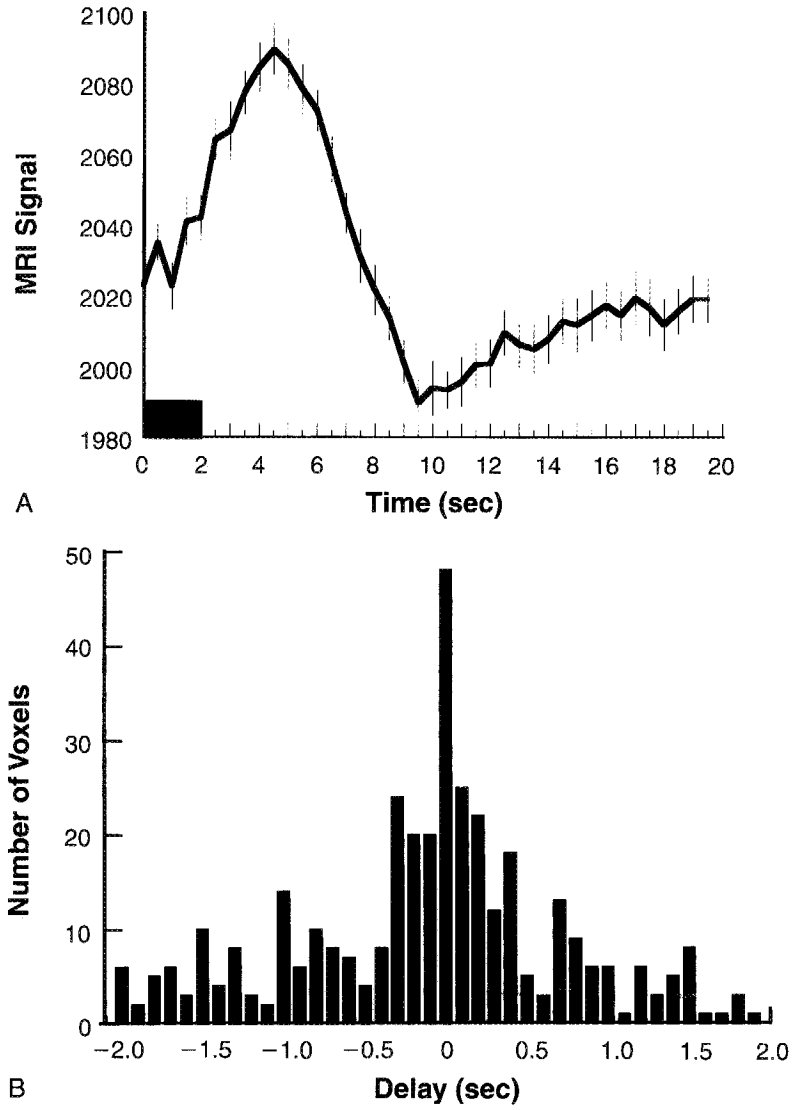

Figure 5. Demonstration of the limits of fMR imaging temporal resolution. Echo planar imaging was performed at 3 Tesla using a Bruker Biospec 3T/60 equipped with a local head gradient coil. A time course series of axial images (matrix size = 96 × 96; FOV = 20 cm; TE = 40 ms; TR = 500 ms; flip angle = 80°) through the motor cortex was obtained. Bilateral finger tapping was performed for 2 sec, alternating with 18 sec rest. These figures demonstrate that the upper temporal resolution is determined by the variability of the signal change in time and space. *A*, Time course of the signal elicited by tapping fingers for 2 sec. The standard deviation at each point was in the range of 1% to 2%. The standard deviation of the hemodynamic change, in time, is in the range of 200 ms to 500 ms. *B*, Histogram of relative hemodynamic latencies. This was created from the latency map shown in Color Plate 2, Figure 11.

suggests that the blood oxygenation increases that occur on brain activation are more extensive than the actual activated regions.[76, 86, 121, 123, 180] In other words, it is possible that although the local oxygenation may be regulated on a submillimeter scale, the subsequent changes in oxygenation may occur on a larger scale due to a "spill-over" effect. An effective counter measure for the "spill-over" is mentioned in the section on latency tagging, which

maintains a constant "spill-over" by always keeping stimuli "on," yet spatially modulated within a region, therefore discriminating subtle differences in activation within a large and less localized "umbrella" of increased oxygenation.

In general, to achieve the goal of high spatial resolution fMR imaging, a high functional contrast-to-noise and reduced-signal contribution from draining veins is necessary. Greater hemodynamic specificity, accomplished by proper pulse sequence choice (selective to capillary effects), innovative activation protocol design (phase-tagging), or proper interpretation of signal change latency (latency mapping), may allow for greater functional spatial resolution. If the contribution to activation-induced signal changes from larger collecting veins or arteries can be easily identified or eliminated, then not only will the confidence in brain activation localization increase, but also the upper limits of spatial resolution will be determined by scanner resolution and functional contrast-to-noise rather than variations in vessel architecture.

Currently, voxel volumes as low as 1.2 μL have been obtained by functional FLASH techniques at 4 Tesla,[183] and experiments specifically devoted to probing the upper limits of functional spatial resolution using spiral scan techniques have shown that fMR imaging can reveal activity localized to patches of cortex having a size of about 1.35 mm.[67] These studies and others using similar methods[55, 56, 67, 168, 170] have observed a close tracking of MR signal change along the calcarine fissure as the location of visual stimuli was varied.

The voxel dimensions typically used in single-shot EPI studies are in the range of 3 to 4 mm, in plane, and having 4- to 10-mm slice thicknesses. These dimensions are determined by practical limitations, such as readout window length, sampling bandwidth, limits of dB/dt (change in magnetic field over time), SNR, and data storage capacity. Other ways to bypass the practical scanner limits in spatial resolution include partial k-space acquisition[46] and multishot mosaic or interleaved EPI.[35, 46, 132] In many fMR imaging situations, multishot EPI may be the optimum compromise between spatial resolution, SNR, and temporal resolution for fMR imaging.

Dynamic Range

Although it is important not to interpret spatial differences in fMR imaging signal change magnitude as indications of differences in the degree of neuronal activation (because the signal is highly weighted by hemodynamic factors such as the distribution of blood volume across voxels), observation of differences in the fMR imaging signal change in the same regions, but across incrementally modulated tasks, is possible, and may be a useful method for extracting more direct neuronal information from the fMR imaging time course series.

The first demonstration that fMR imaging response is not simply binary was made by Kwong et al.[118] Both flow- and oxygenation-sensitized MR signal in V1 were measured as flicker rate was modulated. The signal behavior corresponded closely with that obtained with a previous PET study.[71] Other studies have revealed a responsivity in higher visual areas to contrast and flicker rate.[54, 178] In the primary motor cortex a linear signal dependence on finger tapping rate has been demonstrated.[154] In the primary auditory cortex, a sublinear dependence on syllable presentation rate has been demonstrated.[21]

Sensitivity

Extraction of a 1% signal change (typical of fMR imaging) against a backdrop of motion, pulsation, and noise requires careful consideration of the variables which influence the signal detectability. These variables range from factors that increase signal, increase fMR imaging contrast, reduce physiologic noise, and reduce artifactual signal changes. Following is a list of some salient variables that are important to consider in relation to optimization of fMR imaging sensitivity.

Averaging. Averaging of sequentially obtained images increases the signal-to-noise by the square root of the number of images collected. A difficulty is that if averaging is performed over too long of a period (over about 5 minutes), systematic artifacts (i.e., slow movement or drift) tend to outweigh the benefits obtained from averaging for that duration.

Field strength. As previously discussed, signal-to-noise and functional contrast increase with field strength. Difficulties such as increased shimming problems, increased physiologic fluctuations, and limitations on the possible RF coils used also increase with field strength. It has yet to be

determined if gains in sensitivity obtained by increasing field strength cannot be achieved by other methods at lower fields, or if the gains in sensitivity outweigh the disadvantages of imaging at high field strengths. Figure 6 shows a mosaic of anatomical images and functional contrast-to-noise images obtained of the same axial slice and same subject at different field strengths and different TE values.[13] All images were obtained using single-shot EPI with a local head gradient coil, TR = 1 second, thickness = 5 mm, matrix size = 64 × 64, FOV = 24 cm. The task was bilateral finger tapping. Note that, as expected, the contrast-to-noise appears to be maximum at about the TE = T2* at each field strength. A general increase in contrast-to-noise is observed with field strength.

Filtering. In most fMR imaging studies using EPI, the noise over time is dominated not by system noise, but by physiologic fluctuations. These fluctuations correspond with specific frequencies (i.e., heart and respiration rates). Filtering out of these frequencies can increase the functional contrast-to-noise ratio, or at least make the noise closer to Guassian so that parametric statistical tests can be applied.

Gating. Gating is a powerful technique with one serious drawback that has one potentially powerful solution. Gating involves triggering of the scanner to the heart beat so that an image is always collected at specific phase of the cardiac cycle. This is advantageous because a primary source of noise is collection of images at different phases of the cardiac cycle, causing head misregistration (the brain moves with every heart beat) and pulsatile flow artifacts. Image collection at a single phase would eliminate this misregistration, thereby reducing the noise and potentially increasing the spatial resolution of fMR imaging (i.e., the brain would be imaged at a single position all of the time). The drawback to gating is that if the heart rate changes during the collection of images, the MR signal intensity also changes, depending on the tissue T1 and the average TR used. This generally causes very large fluctuations in the data, making gating relatively worthless in the context of fMR imaging. A technique has recently been developed to correct for the global fluctuations that occur with heart rate changes,[85] therefore making gating a feasible option in fMR imaging. Gating would be especially useful for identifying activation in structures at the base of the brain because that is where pulsatile motion is greatest, where activation is most subtle, and where activated regions are the smallest, requiring the most consistent image-to-image registration.

Paradigm timing. The choice in fMR imaging timing is usually determined by the sluggishness of the hemodynamic response (it usually is not useful to go much faster than an on-off cycle of 8 seconds on and 8 seconds off), the particular brain system that is being activated (cognitive tasks may have a more delayed response), and the predominant frequency power of the noise. As a rule of thumb, the goal is to maximize both the number of on-off cycles and amplitude of the cycle to maximize the power of post-processing techniques, such as correlation analysis,[6] to extract functional information. Generally, contrast-to-noise ratio is maximized and artifact is minimized by cycling the activation of the highest rate that the hemodynamics can keep up with and by having a time course series no longer than about 3 to 4 minutes long.

Post-processing. Many approaches have been used to extract from fMR imaging data estimates of the significance, amplitude, and phase of the functional response, and there is still surprisingly little agreement on the appropriate techniques. If one knows exactly the shape and phase of the expected signal response, a matched filter (i.e., correlation) approach may be optimal. If the shape is unknown, use of a single expected response function, be it a boxcar function or a sine wave, may miss unique activation patterns. The challenge of accurately determining regions of significant activation from fMR imaging data is nontrivial, and has yet to be solved. Some of the developments addressing this issue include the development of accurate and robust motion correction[78, 197] or suppression methods, the determination of the noise distribution,[55, 108, 187] the determination of the temporal[77] and spatial[44] correlation of activation-induced MR signal changes and of baseline MR signal, the

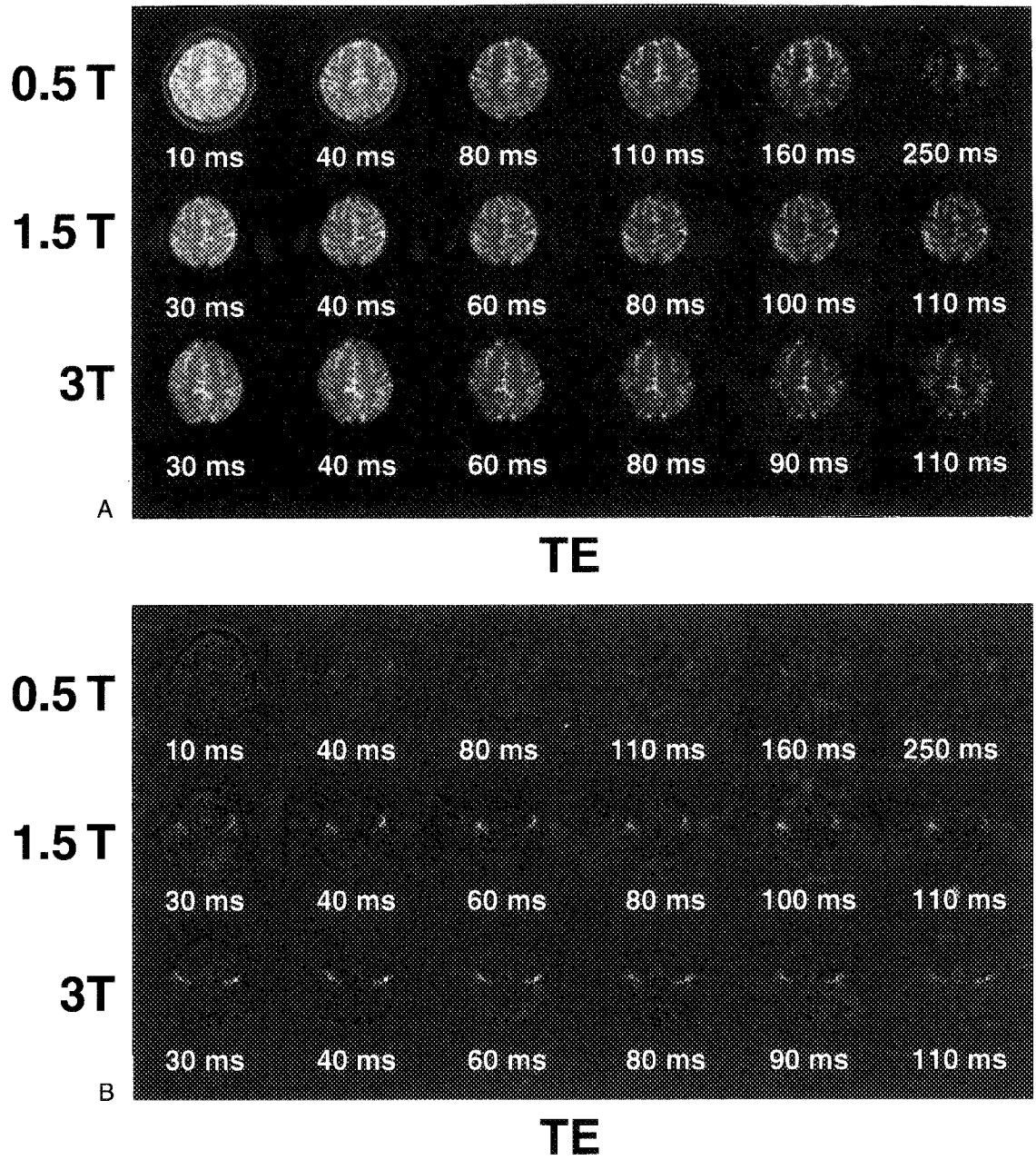

Figure 6. Axial echo-planar images of the same subject across three field strengths (0.5 T, 1.5 T, and 3 T). The scanners were a GE Signa 0.5 T and 1.5 T and a Bruker Biospec 3T/60. The same gradient-coil was used for performance of EPI on each scanner. Pulse sequences were also nearly identical. The image parameters were: FOV = 24 cm; matrix size = 64 × 64; slice thickness = 5 mm; TR = 1 sec; flip angle = 90°. TE was varied for each time course series, which included 200 to 250 images. The task was bilateral finger tapping for 20 sec on / 20 sec off cycles. *A*, The first anatomical images in the time course series. TR = ∞. Note that the MRI signal decay is much slower at 0.5 T than at 3 T. *B*, Functional contrast to noise images corresponding to the anatomial images shown in A. Note that the contrast to noise appears to reach a maximum at each field strength when the TE is approximately equal to the T2 of gray matter, which is about 125 ms, 80 ms, and 50 ms for 0.5 T, 1.5 T, and 3 T, respectively. Improvements in contrast to noise are apparent with field strength. What is not apparent is if the gains at 3 T are critical to perform certain types of fMR imaging studies.

characterization or assessment of the temporal behavior or shape of activation-induced signal changes,[20, 21, 24, 55, 57] and the characterization of how the previously mentioned factors vary in time, space,[123, 124] across tasks,[24, 55, 57] and with different pulse sequence parameters.[118] It is generally important to always inspect the data for motion and not to assume too much about the expected response, yet, at the same time, use all of the current a priori information about hemodynamic responses and neuronal activation to extract meaningful information.

Pulse sequence. Pulse sequences that can be used for fMR imaging have a wide range of sensitivities, with gradient-echo sequences being the most sensitive and time efficient. Standard clinical multishot techniques (i.e., FLASH or gradient echo at steady state [GRASS]) suffer from significantly more motion-related noise than EPI techniques or spiral multishot techniques.[81, 141, 142] Also, application of navigator echoes[98, 141] or other types of image reconstruction-related post-processing of multishot data can significantly reduce artifactual fluctuations.

RF coil choice. The tradeoff here is regarding spatial coverage versus sensitivity. The smaller the coil used, the less brain tissue it couples to. This gives a higher signal-to-noise, but much less brain coverage. Larger RF coils give more brain coverage, but lower signal-to-noise. Where sensitivity is critical, a surface coil in a specific region may be desirable. Where whole-brain imaging is desirable, a whole-brain quadrature RF coil is optimal.[194] This coil is generally as close to the head as possible and couples only to brain region. It should be noted that typical whole-head and neck coils used clinically are suboptimal for whole-brain fMR imaging, because they couple also to the face and neck regions (only adding noise) and because they are generally not as close as possible to the head.

Voxel size. The signal-to-noise is directly proportional to voxel volume. Functional contrast-to-noise is optimized by matching the volume of the active region to the voxel volume. Because functional region sizes are not well characterized and are likely to vary widely, the optimal voxel size is difficult to predict. Many have generally matched the voxel slice to the cortical thickness. Other groups have used a slightly thicker slice to increase brain coverage given a limitation in the number of slices obtainable. Spatial resolution may actually be reduced with the use of smaller voxels if the contrast-to-noise is not high enough to detect more subtle capillary effects. In such a case of low contrast-to-noise, primarily downstream draining veins would be detected. This phenomenon may explain the exclusive detection of large vessels by Lai and Haacke et al[86, 121] using small voxels. Overall, small voxels are desirable as long as the sensitivity remains high enough to detect a 1% signal change.

Some Unknowns

Although not directly related to the practical implementation of fMR imaging, some unexplained and controversial fMR imaging data can give an indication of possible directions that fMR imaging research and applications may take in the future. Listed are four "controversial" results accompanied by the hypotheses related to them:

1. Post-undershoot.[75, 118, 143, 177] After cessation of activation, the BOLD-weighted fMR imaging signal is commonly observed to undershoot the previous baseline signal intensity. The undershoot has been observed to last between 30 seconds and 2 minutes; the reasons for this are unclear. Two hypotheses have been suggested. The first is that on cessation of activation, neuronally triggered flow returns to baseline, but oxidative metabolic rate continues for several minutes, causing a reduction of signal (increased deoxyhemoglobin). The second hypothesis is that on cessation of neuronal stimulation, flow and oxygenation return to baseline levels, but blood volume (possibly pooling in draining veins) takes longer to return to baseline levels, causing the signal to dip below baseline for a small amount of time. As a side note, the post-activation undershoot is not observed using T1-weighted (flow-weighted) sequences.[118]
2. Pre-undershoot.[93, 134] This phenomenon is observed less frequently. Observations by Hennig et al[93] show a dip at 0.5 second.

Observations of Menon et al show a dip at 2 seconds, in agreement with reports of Grinvald et al[84] using optical imaging. Menon et al has put forth a hypothesis that is similar to that of Grinvald et al[84]—that on activation, an increase in oxidative metabolic rate occurs before a subsequent increase in flow. The observations of Hennig et al not only differ in relative timing, but also differ in the hypothesized origin. The signal is found to be only slightly T2* (oxygenation)-related, and primarily T1-related. The hypothesis is that changes in the ionic environment of the neurons caused by the influx of Na^+ may rapidly change the T1 of the tissue.

3. Long-term effects.[7-9, 11, 75, 90] The effect of sustained activation on fMR imaging signal intensity is controversial. Three studies with differing results have been reported. Hathout et al[90] have suggested that local blood oxygenation returns from an initially elevated level to baseline after about 15 minutes of continuous stimulation. Frahm et al[75] have observed a return of oxygenation-sensitive MR signal to baseline after about 1 to 2 minutes of sustained activation, but has also observed sustained blood flow during the entire stimulation duration.[73] Bandettini et al[7-9, 11] have demonstrated sustained flow and BOLD enhancement for entire stimulation durations. Stimulation durations were up to 20 minutes long. Possible explanations for these differences in results include differential effects of the particular stimuli on metabolic, hemodynamic, or neuronal changes or differential, and not fully understood pulse sequence sensitivities.
4. Noise correlation.[27] This observation is that the noise in the fMR imaging data obtained during a resting state shows temporal correlation across regions that appear to be functionally connected (i.e., motor cortex). The predominant frequency that shows most correlation is in the 0.1 to 0.2 Hz range. The origin of these suggests an oscillation in vascular tone that is synched across similar functional units in the brain. These findings may be clinically useful in determining vascular tone and/or diagnosing cerebrovascular pathologies.

COMMON fMR IMAGING PLATFORMS

In an attempt to bring much of what has been mentioned together, this section describes some of the most commonly used platforms for fMR imaging. The three types of fMR imaging pulse sequences discussed are EPI, conventional multishot imaging, and spiral scanning.

EPI

EPI is an ultra-fast MR imaging technique[46, 63, 128, 175] that has been, and continues to be, ubiquitous in the ongoing development and application of fMR imaging. In most of the growing number of centers that have EPI capability, it is the fMR imaging method of choice for most applications. Some centers that have been using EPI for fMR imaging of humans include Massachusetts General Hospital, Medical College of Wisconsin, Yale, University of California, San Diego, National Institutes of Health, Michigan State, Pittsburgh, Mayo Clinic, Duke, University of Minnesota, University of Wisconsin, Beth Israel Hospital in Boston, Hammersmith Hospital in London, University of Nottingham, and University of California, Los Angeles.

EPI has several drawbacks, including low spatial resolution, high sensitivity to off-resonance effects, need for specialized hardware, potential for peripheral nerve stimulation, and need for specialized image reconstruction algorithms. The advantages of EPI, which include high temporal resolution, high flexibility for imaging several types of physiologic processes, high stability, low imaging duty cycle, and low sensitivity to motion, still greatly outweigh the disadvantages for most purposes related to fMR imaging. To follow is a brief description of some of these EPI characteristics.

Spatial resolution in single-shot EPI is limited either by the area of k-space that can be sampled in approximately one T2* period or by the system bandwidth.[69] The area of k-space that can be covered can be limited by the velocity in k-space (gradient amplitude) or the acceleration in k-space (gradient slew rate), and is typically limited by both.

The requirement, with EPI, for strong and rapidly switching gradients is satisfied by in-

creasing the gradient amplifier power or by using a speed-up circuit, implementing resonant gradient technology, reducing the inductance of the gradient coils such that they can be driven by conventional gradient amplifiers, or increasing the field of view or lowering the resolution to match the speed at which standard gradient amplifiers can keep up.

The first strategy is probably among the least commonly used. GE Medical Systems (Milwaukee, WI) and Siemens Medical Systems (Erlangen, Germany) are currently marketing systems using this technique. The second strategy is likely to be the most common EPI technique as of yet (it has been commercially available for the longest time). Advanced NMR (with GE Medical Systems) and Siemens have been marketing this technology for several years. Both strategy 1 and 2 use whole-body gradient coils, which allows performance of EPI for functional or kinematic studies on the heart, lungs, digestive system, kidneys, throat, joints, and muscles. In the context of fMR imaging, whole-body gradients allow more accessibility for patients with mobility problems and for easy delivery of brain activation stimuli.

The third strategy is used primarily by several centers that have home-built gradient coils (two examples are National Institutes of Health[181] and the Medical College of Wisconsin[193]) marketed by Medical Advances in Milwaukee, Wisconsin (using the coil design of E.C. Wong), Advanced NMR, and Siemens, among others. This strategy is implemented by using a gradient coil that is localized only to the head. The gradient fields are optimized for a region that usually covers the brain or the region of RF sensitivity.

Lastly, single-shot EPI can be carried out on a conventional imaging system without the use of local gradient coils (using the whole-body gradient coil) by simply using a large FOV or a small image matrix size.[28] fMR imaging using EPI with voxel sizes of approximately 10 mm × 10 mm × 10 mm (approximately the resolution of a PET scanner) has been successfully performed on a standard GE 1.5 Tesla Signa system[197] with excellent results. This type of echoplanar imaging capability exists on practically every clinical scanner in the world.

A major nonhardware-related limitation on gradient slew rate is the biological threshold for neuronal stimulation due to time-varying magnetic fields. At present, high-performance gradient systems (either local gradient coils or high-powered whole-body systems) are capable of exceeding the Food and Drug Administration guidelines on gradient field slew rate (dB/dt). This is a large determinant of the upper limit on the resolution possible using single-shot EPI to image humans.

The requirements for successful implementation of EPI for fMR imaging are not limited to hardware. In most cases, phase correction algorithms applied during image reconstruction are usually necessary to compensate for timing errors related to imperfections in gradients, gradient-induced eddy currents, or static field inhomogeneities.

Because of the long sampling time and artifactual phase modulation, EPI is sensitive to two types of off-resonance–related artifacts in EPI: signal dropout and image distortion. Signal dropout is primarily due to intravoxel phase dispersion resulting from through plane variation of magnetic field. The problem of signal dropout in gradient-echo sequences can be reduced by reduction of the TE, reduction of the voxel volume, or by localized shimming. Also, this effect is greatly reduced in spin-echo EPI because the macroscopic off-resonance effects are refocused at the echo time.

Image distortion is caused by an off-resonance–related phase modulation that occurs during data acquisition. In EPI, this linear phase modulation creates primarily a linear distortion of the image in the phase encode direction. Several post-processing methods have been put forward for correcting image distortion in EPI.[105, 186]

With the use of EPI, approximately 10 images may be obtained per second, giving the option to image the entire brain in under 2 seconds or to sample a smaller number of imaging planes to allow a more dense sampling of the time course. Another possibility in EPI is to sample less densely in space, but to cover a large volume in a single shot; this technique is known as echo-volume imaging (EVI).[128, 172]

A practical but significant factor to be considered when performing fMR imaging with EPI is the rapidity with which large amounts of data are collected. This data may then go through several additional transformations (adding to the total required data storage capacity) before a functional image is created. If 10 slices having 64 × 64 resolution are acquired every 2 seconds (typical for multislice fMR imaging), then the data acquisition rate is approximately 2 MB per minute.

Conventional Multi-shot Imaging

High-temporal-resolution fMR imaging techniques developed for use with conventional gradients include multishot FLASH,[38, 49, 51, 62, 73, 121, 148] turbo-FLASH,[97] low-resolution EPI,[29, 192] multishot or interleaved EPI,[35, 132] echo-shifted flash,[126, 137] keyhole imaging,[171] and fast spin-echo.[50]

Only a few centers have been able to successfully implement conventional multishot techniques in a routine and robust manner for fMR imaging.[62, 73, 86, 183] The advantage to multishot techniques is the ability to achieve relatively high in-plane spatial resolution, less sensitivity to off-resonance effects from poor shim, and the availability of the technique on most clinical scanners. The disadvantages are lower temporal resolution, increased noise due to nonrepeated shot-to-shot misregistration of k-space lines[81, 141, 142] (from variable sampling of low-frequency lines at different phases of the cardiac cycle), lower signal due to the need for short TR and low flip angles, reduced capability to perform multislice fMR imaging as rapidly as with EPI, and less flexibility or "dead time" (that comes with a long TR typically used for EPI) for other types of pulse sequence manipulations. More time-efficient and stable multishot techniques include fast spin echo[50] and spiral scan imaging.[81, 141, 142]

Spiral Scanning

Of non-EPI techniques, multishot spiral-scan sequences used in conjunction with a single-point phase correction scheme have demonstrated the most temporal stability.[82, 142] Spiral scanning also involves oversampling at the center of k-space, where the acquisitions are intrinsically gradient-moment nulled, providing less sensitivity to phase errors caused by brain, blood, or cerebral spinal fluid pulsations with the cardiac cycle.

Spiral scanning has been used for many fMR imaging applications,[43, 44, 67, 168] and when used in conjunction with a phase-tagging activation scheme, has demonstrated the highest functional resolution (1.35 mm) to date.[67] In studies where high spatial resolution is important or where EPI is unavailable, spiral scan appears to be the method of choice.

Figure 7 shows a comparison between spiral scan and EPI. Single-shot EPI (TE = 40 ms, TR = 1 second, flip angle = 90 degrees) is compared with 10-shot spiral scanning (TE = 30 ms, TR = 250 ms, flip angle = 30 degrees). The EPI anatomical images show distortion relative to the spiral scan images, which are distortion-free. The contrast-to-noise images indicate similar areas of activation and similar regions of highest signal changes, likely to be large veins. With these parameters, no additional inflow effects were observed in the functional images obtained using spiral scanning. Note also that in the spiral scan anatomical image, dark spots appear in the same region as the areas of greatest activation. These dark areas may be regions of significant intravoxel dephasing in the vicinity of veins, as described by Haacke et al.[86]

APPLICATIONS

Most studies involving the development of fMR imaging from a contrast mechanism, pulse sequence, and post-processing standpoint have used primary motor and visual cortex activation due to the easily elicited and robust signal changes. Following are some of the applications of fMR imaging that have gone beyond simple finger tapping or visual stimulation. The auditory cortex,[22, 23] somatosensory cortex,[88, 163] and cerebellum[66] have been studied. Detailed mapping of regions activated in the primary motor cortex[39, 102, 110, 112, 154, 156] and visual cortex[55, 56, 58, 67, 168] have been performed as well. Activity elicited in the gustatory cortex has been mapped.[52] Other studies using fMR imaging have observed organizational differences related to handedness.[111] Activation changes during motor task learning have been observed in the primary motor cortex[107] and cerebellum.[65] Cognitive studies in normal subjects have included word generation,[18, 95, 130, 162] mental rehearsal of motor tasks and complex motor control,[113, 155] visual processing,[55, 167, 174] speech perception,[22, 23] semantic processing,[19, 23, 25] working memory,[43] visual recall,[122] and mental rotation.[47]

Studies have also been performed involving specific pathologies. Abnormal connectivity of the visual pathways in human albino volunteers has been demonstrated.[92] Changes in organization in the sensorimotor area after brain

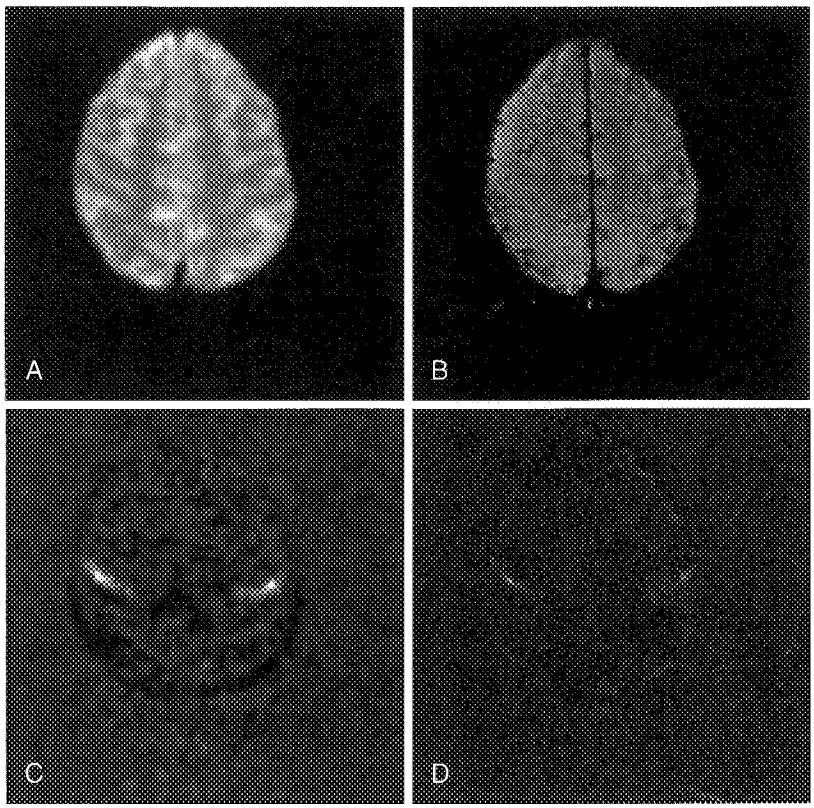

Figure 7. Anatomical and functional imaging comparison. Echo planar imaging and spiral scanning. *A*, Single shot EPI obtained on a Signa 1.5 T scanner retrofitted with an ANMR resonant gradient system. FOV = 20; Matrix size = 64 × 64; TE = 40 ms; TR = ∞; flip angle = 90°. Echo planer images generally show distortion in the phase encode direction in the presence of off resonance effects. *B*, Ten shot (or interleave), spiral scan image. FOV = 20 cm; Matrix size (after reconstruction) = 131 × 131; TE = 30 ms; TR = 250 ms; flip angle = 30°. Spiral scan images do not show distortion but, in the presence of off resonance effects, they show blurring. *C*, Functional contrast to noise image created from the spiral scan time series. *D*, Functional contrast to noise image created from the EPI time series (TR = 1 sec). Comparison of the two contrast to noise images indicate similar areas of activation and similar regions of highest signal changes—likely to be large veins. With these parameters, no additional inflow effects were observed in the functional images obtained using spiral scanning.

injury have been observed.[39] One study has demonstrated larger fMR imaging signal changes, on the average, in schizophrenic patients.[157] The ability to localize seizure activity has also been demonstrated by fMR imaging.[103] In addition, preliminary data demonstrating the effects of drugs on brain activation have been presented.[189] Activity associated with obsessive-compulsive behavior has also been observed.[32, 33]

The immediate potential for clinical application is currently being explored. "Essential" areas of the sensory and motor cortex, as well as language centers, have been mapped using both fMR imaging and electrical stimulation techniques.[37, 102, 153] Activity foci observed across the two methods have shown a high spatial correlation, demonstrating the potential for fMR imaging to complement or replace the invasive technique in the identification of cortical regions that should be avoided during surgery. In the context of presurgical mapping, fMR imaging has demonstrated the ability to reliably identify the hemisphere where language functions reside,[18, 19, 23, 25] potentially complementing or replacing the Wada test (hemisphere specific application of an anesthetic amobarbital) for language localization that is

also currently used clinically prior to surgery.[139] Several review articles and chapters on fMR imaging techniques and applications are currently available.[2, 4, 5, 9, 19, 43, 45, 149, 152, 167, 169, 179]

CONCLUSIONS

Since its start in 1991, fMR imaging has been evolving rapidly into a highly robust and widely used technique. It is wrought with technical difficulties, most fully solvable. Alternatively, it is likely to have at least several uses that have not yet been uncovered. First reviewed in this article were the current types of hemodynamic contrast available with fMR imaging, with emphasis on the newest and most promising technique of quantitative blood flow mapping. Second, the ubiquitous issues of fMR imaging, including interpretability, sensitivity, and some current unknowns, were described in detail. Third, common fMR imaging platforms, with emphasis on hardware and pulse sequence issues, were described. Lastly, the ever-growing clinical and research applications were outlined. The basic principles, practicalities, and potentials of the array of techniques known as fMR imaging (as of April 1996) have been described. It is hoped that the reader will come away with a more clear prospective of this intricate, technically challenging, complicated, yet robust and truly exciting, new brain imaging technique.

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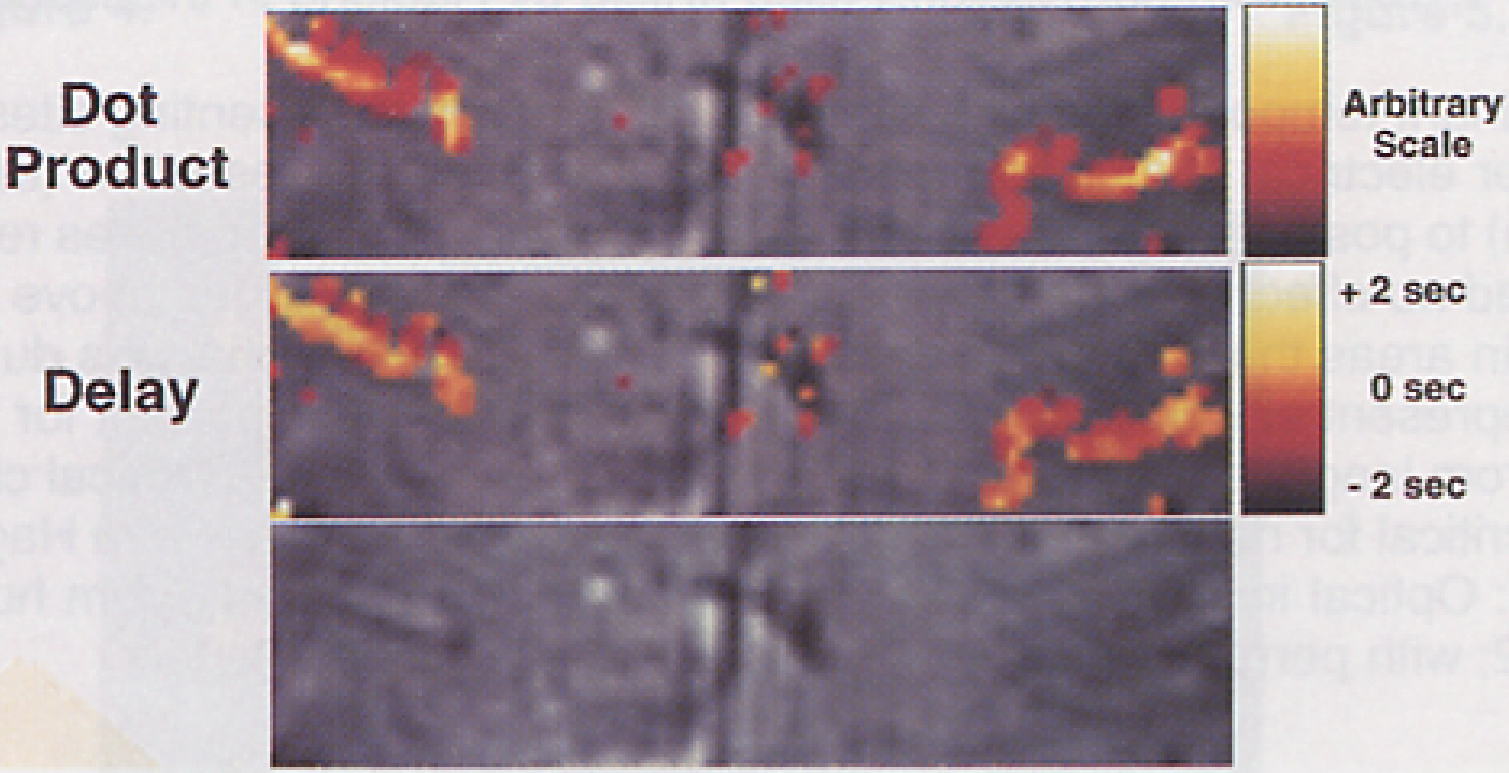

Figure 11.

Figure 11. Map of the dot product (a measure of the activation-induced signal change magnitude), and the relative latencies or delays of the reference function at which the correlation coefficient was maximized. The spatial distribution of hemodynamic delays has a standard deviation of about 900 ms. The longest delays approximately match the regions that show the highest dot product, and the area where veins are shown as dark lines in the T2* weighted anatomical image. (See article by Bandettini and Wong in this issue.)